REMARKS

Claims 18 and 19 are pending in the subject application. No claim has been added, canceled, or amended herein. Accordingly, claims 18 and 19 are still pending and under examination.

In view of the arguments set forth below, applicants maintain that the Examiner's objection and rejection made in the November 19, 2004 Final Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw same.

Rejection Under 35 U.S.C. §103(a)

The Examiner rejected claims 18 and 19 under 35 U.S.C. §103(a) as allegedly unpatentable over D'Apuzzo et al. ("D'Apuzzo") in view of Gerard et al. ("Gerard").

In response to the Examiner's rejection, applicants respectfully traverse.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, must teach or suggest each element of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

Here, the references cited against the rejected claims fail to support a *prima facie* case of obviousness, because they do not teach or suggest every element of the claimed invention, and do not create a motive to combine or an expectation of success.

Claims 18 and 19 provide an assay for determining whether a non-peptidyl agent inhibits the activation of a CXCR4 receptor by the chemokine, stromal cell-derived factor 1 ("SDF-1"). These claims are based, at least in part, upon applicants' surprising discovery that SDF-1 is specifically overexpressed in cultured synoviocytes derived from joints affected by rheumatoid arthritis. According to the specification, it was "discovered that SDF-1 is expressed on the synoviocytes which can activate the [CXCR4] receptors on lymphocytes and monocytes, either causing them to enter the joint and initiate inflammation through a chemokine effect, or activate these cells that have entered the joint to enhance inflammation." (page 3, lines 32-37). Further, based on their discovery, applicants stated that "[w]e speculate that the production of SDF-1 by intimal synoviocytes in the normal joint could act as a guidance cue for the continual entrance into the intimal synovial membrane of monocyte lineage precursors committed to differentiation into phagocytic lining cells. Similarly SDF-1 and other chemokines elaborated by the normal synoviocytes may act to enhance the ingress of lymphocytes into the joint tissues to facilitate physiologic surveillance functions." (pages 20, lines 18-26).

Accordingly, the invention can be practiced to identify non-peptidyl agents which can block the interaction of SDF-1 with its receptor, CXCR4, on peripheral immune cells infiltrating the joint, thereby treating rheumatoid arthritis.

In support of the rejection, the Examiner has cobbled together the teachings of two references with the advantage of hindsight as to applicants' unexpected discovery.

Specifically, the Examiner stated that D'Apuzzo teaches that anti-CXCR4 antibody inhibits activation of CXCR4 receptor by SDF-1, wherein the B cell response requires CXCR4 activation to take place. The Examiner conceded that D'Apuzzo alone does not teach such method with a non-peptidyl agent, as taught by the subject invention. However, the Examiner asserted that Gerard discloses that nonpeptide inhibitors of chemokine function are well known in the art as is the desirability to identify such compounds. The Examiner further stated that although Gerard largely addresses the chemokine receptor CCR3, it would have been equally desirable to screen for inhibitors of CXCR4 for the same reasons that it was desirable to screen for inhibitors of CCCR3. Therefore, the Examiner asserted that it would have been *prima facie* obvious to one of ordinary skill in the art to have created the claimed invention because D'Apuzzo et al. teach the claimed method except for use of the assay to screen non-peptidyl agents and Gerard et al. disclose that non-peptide inhibitors of chemokine function are

well known in the art as is the desirability to identify such compounds.

Applicants maintain that the cited references, in combination, fail to teach all elements of the instant method. Specifically, applicants note that Gerard differentiates the chemokine receptor family into two distinct branches, the C-C chemokines, wherein the first two conserved cysteines are adjacent, and the C-X-C chemokines, wherein the first two conserved cysteines are separated by an intervening residue. (see column 1, lines 43-49). Furthermore, Gerard only teaches that "C-C chemokines are of great interest because of their potential role in allergic inflammation." (column 2, lines 1-2, emphasis added). Gerard fails to teach or suggest any inhibitors of C-X-C chemokines, such as CXCR4, and fails to teach that such inhibitors are of interest. A skilled artisan would recognize that the teaching of Gerard is, at most, restricted to C-C chemokines and that inhibitors of C-X-C chemokines, such as CXCR4, are neither taught nor suggested. Therefore, one of ordinary skill in the art would not arrive at the subject invention by combining the teachings of Gerard et al. (i.e. non-peptide inhibitors of C-C chemokine receptors, such as CCR3, exist) with the teachings of D'Apuzzo et al. (i.e. anti-CXCR4 antibody inhibits activation of CXCR4 by SDF-1) nor would she be motivated to try or reasonably expect success.

For the reasons above, the cited references combined fail to teach the elements of the claimed assay. Absent such teaching, there could not have been a motive to combine or a reasonable expectation of success.

In view of the above remarks, applicants maintain that the Examiner has failed to set forth a *prima facie* case of obviousness, and that accordingly, claims 18 and 19 satisfy the requirements of 35 U.S.C. §103(a).

Summary

Applicants maintain that the claim pending is in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Communication. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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